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Original Article

Trisodium citrate 4%—an alternative to heparin capping of haemodialysis catheters

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Abstract

Background. Central venous catheters (CVCs) continue to be used at a high rate for dialysis access and are frequently complicated by thrombus-related malfunction. Prophylactic locking with an anticoagulant, such as heparin, has become standard practice despite its associated risks. Trisodium citrate (citrate) 4% is an alternative catheter locking anticoagulant.

Methods. The objective was to prospectively study the clinical effectiveness, safety and cost of citrate 4% *vs* heparin locking by comparing rates of CVC exchanges, thrombolytic use (TPA) and access-associated hospitalizations during two study periods: heparin period (HP) (1 June 2003–15 February 2004) and Citrate Period (CP) 15 March–15 November 2004. Incident catheters evaluated did not overlap the two periods.

Results. There were 176 CVC in 121 patients (HP) and 177 CVC in 129 patients (CP). The event rates in incident CVC were: CVC exchange 2.98/1000 days (HP) *vs* 1.65/1000 days (CP) ($P = 0.01$); TPA use 5.49/1000 (HP) *vs* 3.3/1000 days (CP) ($P = 0.002$); hospitalizations 0.59/1000 days (HP) *vs* 0.28/1000 days (CP) ($P = 0.49$). There was a longer time from catheter insertion to requiring CVC exchange ($P = 0.04$) and TPA ($P = 0.006$) in the citrate compared with the heparin lock group. Citrate locking costs less than heparin locking but a formal economic analysis including indirect costs was not done.

Conclusion. Citrate 4% has equivalent or better outcomes with regards to catheter exchange, TPA use and access-related hospitalizations compared with heparin locking. It is a safe and less expensive alternative. Randomized trials comparing these anticoagulants with a control group would definitively determine the optimal haemodialysis catheter locking solution.

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Keywords: citrate; haemodialysis catheters; heparin; TPA

Background

Since the early 1980s, when the first double lumen central venous catheters (CVCs) were introduced for haemodialysis (HD) vascular access [1], they continue to be used at a high rate despite national guidelines recommending the contrary [2,3]. Up to 70% of North American patients initiate HD with a CVC and a further 40% continue to use it 90 days after dialysis initiation [4,5]. A common challenge associated with CVC use is maintaining the intraluminal patency required to provide sufficient blood flow to achieve adequate dialysis. Aside from mechanical disturbances, such as catheter kinks and malposition, the most common cause of intraluminal disturbance resulting in poor blood flow is intraluminal thrombus formation [6]. Once fully formed, the thrombus may be difficult to treat and often requires repeated intervention with thombolytic agents or catheter exchange. The standard prophylaxis for intra-luminal thrombus formation is catheter locking with an anticoagulant, such as heparin.

Heparin is composed of sulphated polysaccharides that undergo a conformational change when it binds with antithrombin III. Its anticoagulant effect occurs through the subsequent inhibition of factor Xa and thrombin II. While heparin has been used as the standard locking solution, usually with an amount based on the capped luminal volume, there are few studies addressing the efficacy or safety of different concentrations of heparin. There is a considerable range in the requirement for thrombolytic agents (3.0–9.5/1000 CVC days) [7–9], a surrogate marker for failure of anticoagulation, which may reflect variation in heparin lock concentrations. Heparin is also associated with potential systemic anticoagulation, heparin induced thrombocytopenia and bleeding risks, especially in uraemic patients already at risk of bleeding [7,10–12].

Trisodium citrate (citrate) 4% has been used as an anticoagulant in blood products, for dialysis and apheresis since 1914 [13,14]. Trisodium citrate acts locally as an anticoagulant by chelating ionized calcium in blood, resulting in the blockage of calcium-dependent clotting pathways. Inter-dialytic citrate locking has been reported in the literature [7,15,16] using full strength or diluting the concentrated formulation (46.7% diluted to 23.3%; 30%) but there are potential risks when used in high concentration [17–19]. Case reports of fatal cardiac arrest following the use of high concentrations of trisodium citrate (i.e. 46.7%) led to the withdrawal of a commercially marketed product, Tricitrosol® by the US Food and Drug Administration (FDA) 5 years ago [20]. In contrast, studies that used a dilute citrate formulation (4%) demonstrated efficacy as an anticoagulant with minimal to no risk of bleeding, but these were small studies with limited generalizability to stable out-patient haemodialysis patients [21–24]. To date, there have been few reported comparisons of its efficacy, safety or cost with heparin locking [25]. In our institution, citrate 4% is less expensive than heparin on a per catheter basis. However, this reduced cost would be misleading should the use of citrate capping be associated with more costly events such as greater TPA use and CVC exchanges due to CVC malfunction. Therefore, we set out to study the clinical effectiveness, safety and cost of citrate 4% *vs* heparin locking in a prospective, longitudinal cohort of HD patients using permanent tunnelled cuffed CVC in our institution. We hypothesized that there would be no difference in thrombolytic use, CVC exchanges and access-associated hospitalizations, thus demonstrating the cost effectiveness of citrate *vs* heparin for CVC locking.

Methods

Study design

This study was planned and implemented as a prospective cohort study from 1 June 2003 to 15 November 2004 within the University Health Network (UHN) haemodialysis programme. This programme manages between 300 and 350 haemodialysis patients and has incorporated a multidisciplinary approach to access management since January 1996 [26]. It consists of a full-time vascular access coordinator, a part-time nurse whose responsibilities include access monitoring, nephrologists, interventional radiologists and vascular surgeons. There is a weekly vascular access clinic and bimonthly interdisciplinary meeting to review and discuss complicated cases.

All chronic haemodialysis patients with a permanent, cuffed internal jugular tunnelled CVC were studied. Our programme primarily used the Uldall-Cook Catheter (Cook Canada Inc.) dual lumen catheter (95%). However, the following dual lumen CVCs may have been used as our programme was randomly sampling other types: HIGHFLOW Dialysis Catheter (CardioMed Supplies Inc., Gormley, ON, Canada), Opti-flow/HemoGlide dual-lumen permanent dialysis catheter (Bard Access Systems, Utah, USA) and Vaxcel® Plus Chronic Dialysis Catheter (Boston Scientific, MA USA). When this was the case, the choice of CVC type and side of insertion was left to the discretion of the radiologist performing the procedure. Catheter exchanges were performed by the interventional radiology department as an out-patient procedure unless the patient was already hospitalized. All filling volumes were documented and acknowledged by the haemodialysis nurse who was responsible for capping the catheters post dialysis. Baseline demographic and access information was collected. The access coordinator prospectively tracked the number of CVC insertions and removals, use of TPA and vascular access-related hospitalizations. All information was entered into a clinically based, centralized vascular access database that is updated daily.

The study defined two study periods: The 'Heparin Period (HP)' (1 June 2003–15 February 2004) that was intended to determine the baseline rate of catheter exchanges, TPA use and access-related hospitalizations using our standard of practice of locking CVC with heparin using 5000 U/lumen total (0.5 ml of a 10 000 unit/ml heparin concentration with normal saline 9% to fill the lumen volume) after each dialysis session. Specifically, after a 10 cc normal saline flush, haemodialysis nurses prepared the heparin solution in a 3 or 5 cc syringe by mixing 0.5 ml of 10 000 U/ml heparin with the required amount of normal saline to fill the catheter lumen and then instilled the solution into each catheter port. All patients were then switched to locking CVC with citrate 4% after each dialysis session, starting on 15 February 2004 ['Citrate Period' (CP)]. Data were collected from 15 March 2004 to 15 November 2004 to evaluate outcomes during the CP. The citrate was provided in 5 ml preloaded syringes, prepared by the on-site pharmacy. While this study involved only permanent catheters, the rare temporary catheters used in the dialysis unit were capped with the same solution used during the study period.

Outcome measures

The primary endpoint of this study was the number of catheter exchanges required/1000 catheter days. The secondary endpoints were the rate of TPA use/1000 catheter days and the rate of access-related hospitalization. The time to catheter exchange and time to TPA requirement, using these locking solutions were also compared. Lastly, the costs of administering heparin *vs* citrate 4% capping irrespective of these endpoints were compared.

Catheters were exchanged when blood flow through the CVC was so limited that the CVC could not provide dialysis and was considered a salvage procedure. All conservative measures to improve catheter patency and function were first attempted. For example, patients were repositioned, had their lines saline flushed and reversed and received TPA. The dialysis nurses were able to administer TPA under a medical directive allowing them to provide TPA to a patient's CVC without doctor's orders, used only in strict accordance with the institutional protocol for TPA administration. Briefly, nurses were trained to perform the conservative manoeuvers noted above to exclude non-thrombus or mechanical problems prior to instituting TPA when peak blood flow rate fell below 250 ml/min or if dialysis adequacy was threatened due to reduced flows that were clinically deemed

related to catheter thrombosis. If the nurses required confirmation prior to using TPA, the attending nephrologist was consulted. It is not logistically or practically feasible in our dialysis unit to routinely send patients to radiology to determine if the cause of catheter malfunction was related to an intraluminal thrombus due to resource and time constraints.

Access-related hospitalizations were all-cause hospitalizations due to catheter complications, such as bleeding, sepsis and those related to catheter insertions or removals.

The costs of heparin *vs* citrate locking were independently determined by the hospital pharmacy and included the cost of the anticoagulant, equipment (e.g. syringes), manpower required to dispense and administer the locking solution. The financial direct and indirect (e.g. rental and equipment costs, professional fees, etc.) costs of catheters, catheter exchanges and hospitalizations did not differ between the two time periods. In this study, only direct cost differences between the two CVC locking solutions were evaluated.

Patients were prospectively followed for the above outcomes in both the HP and CP until the end of the study on 15 November 2004.

Analysis

The primary and secondary endpoints of this study were expressed as events/1000 catheter days. The primary analysis was performed on prospective patients who were in the dialysis unit who had incident catheters inserted during either the HP or the CP and did not overlap study periods. Incident catheters in the HP were censored on 15 February 2004 and those in the CP on 15 November 2004, respectively, if they were still in use at that time. A sensitivity analysis was performed that evaluated only the first incident catheter per patient per study period. Some patients and catheters were prevalent over both study periods 'overlap group'; this group was not evaluated.

Rate specific outcomes (event/1000 CVC days) were compared using the exact binomial test for Poisson distributions (appropriate for rates using person-time denominators). Time to event analyses (catheter exchange and TPA requirement) were estimated using Kaplan–Meire survival curves and compared with the log-rank test. All tests of significance were two-sided, and differences were considered statistically significant with a P-value <0.05. The statistical software used was SAS (version 8.2) (SAS Institute Inc., Cary, NC, USA).

Results

In the total study period, there were 527 CVC used in 347 patients. There were 174 prevalent catheters in 97 patients that were excluded from analysis. The results of the primary analysis in 250 patients and their respective 353 catheters that were independent of each other in the HP or CP are presented. Of these patients, 176 catheters in 121 patients were used during the heparin locking period and 177 catheters in 129 patients during the citrate period. There were no differences in patient characteristics between these groups of patients (Table 1).

Table 1. Patient characteristics

Variable	Heparin	Citrate
N	121	129
Catheter days	16761	17593
Mean age (SD) (range)	60 (16.3) (20–92)	60 (16.0) (22–87)
Sex (% male)	67 (55.4%)	69 (53.5%)
Ethnicity		
Caucasian	72 (59.5%)	74 (57.4%)
Black	19 (15.7%)	13 (10.0%)
Other	30 (24.8%)	42 (32.6%)
Aetiology		
Diabetes	22 (18.2%)	24 (18.6%)
Hypertension	18 (14.9%)	17 (13.2%)
Glomerulonephritis	33 (27.3%)	36 (27.9%)
Interstitial nephritis	3 (2.5%)	2 (1.6%)
Other	28 (23.1%)	33 (25.6%)
Unknown	174 (14.0%)	17 (14.1%)
Comorbidities		
DM	46 (38.0%)	38 (29.5%)
HTN	85 (70.2%)	93 (72.1%)
CAD	30 (25.8%)	33 (25.6%)
CHF	25 (20.7%)	25 (19.4%)
CVA/TIA	10 (8.3%)	14 (10.9%)
PVD	17 (14.0%)	15 (11.7%)
Hyperlipidaemia	28 (23.1%)	38 (29.7%)

DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; CVA/TIA, stroke or transient ischemic attack; PVD, peripheral vascular disease.

In the primary analysis, there were 16 761 catheter days in the HP and 17 593 catheter days in the CP. Subjectively, some nurses and patients noted clots in the dialysers of patients capped with citrate compared with heparin. For this and other reasons, seven patients refused citrate capping and were analysed in the heparin group. The CVC exchange rates were greater for catheters capped with heparin (2.98/1000 CVC days) compared with citrate (1.65/1000 CVC days; $P=0.01$). The proportion of patients requiring at least one catheter exchange was 83% in the heparin group and 67% in the citrate group ($P=0.006$) (Table 2). There was a longer time from catheter insertion to requiring catheter exchange for suspected thrombosis-related malfunction in the citrate locking group compared with the heparin lock group (Figure 1). The TPA rate during HP was 5.49/1000 CVC days and during CP, it was 3.3/1000 CVC days ($P=0.002$). There was a longer time interval before requiring TPA in newly inserted catheters in the CP compared with the HP (Figure 2). The hospitalization rate was 0.59/1000 CVC days in the HP and 0.28/1000 CVC days in the CP ($P=0.49$). The average hospitalization stay was longer in the HP (8.62 days) compared with that in the CP (3.34 days) ($P=0.02$). The majority of hospitalizations during the HP were due to line-related bacteraemias or sepsis while this occurred minimally during the CP. The catheter-related bacteraemia rate was 1.7/1000 CVC days in HP compared with 0.2/1000 CVC days in the CP ($P<0.0001$) in incident catheters. The sensitivity

analysis and outcomes of first catheters per patient per study period demonstrated similar results to the primary analysis. For example, the proportion of patients requiring CVC exchanges was 66% (HP) *vs* 47% (CP), $P = 0.01$ and the TPA rates were 4.51/1000 CVC days (HP) *vs* 1.26/1000 CVC days (CP), $P < 0.0001$. Hospitalization rates were not determined for the first new catheter per patient per period as the numbers were too small ($n = 5$ in each group). No association was found between the varying types of catheters and outcomes (minimum P-value = 0.16; data not shown).

The total cost of preparing and administering heparin capping was $1.68 (Can) and for citrate capping $0.72 (Can).

Table 2. Comparison of outcomes of incident catheters per study period

Outcome	Heparin	Citrate	*P*-value
CVC exchange	2.98/1000	1.65/1000	0.01
Proportion with at least one exchange	83%	67%	0.006
TPA rate	5.49/1000	3.3/1000	0.002
Hospitalization admit	0.59/1000	0.28/1000	0.49
Hospital days	4.12/1000	1.36/1000	<0.001
Mean hospitalization days	8.62	3.34	0.016

Discussion

Our study found that locking tunnelled, cuffed central venous dialysis catheters with trisodium citrate 4% had equivalent or better outcomes compared with inter-dialytic locking with heparin sulphate (5000 U/lumen) with regards to the frequency of catheter exchanges, intraluminal thrombolytic use and access-associated hospitalizations.

The results of our study are consistent with earlier trials of low-concentration citrate catheter locking compared with heparin locking. Two early small, prospective, randomized, non-blinded trials compared citrate to heparin as a lock to maintain single lumen

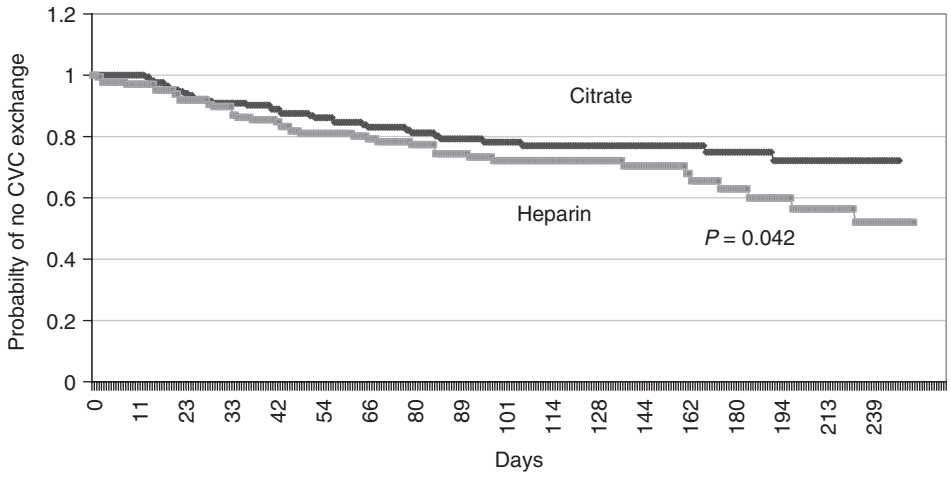

Fig. 1. Time to catheter exchange of incident catheters.

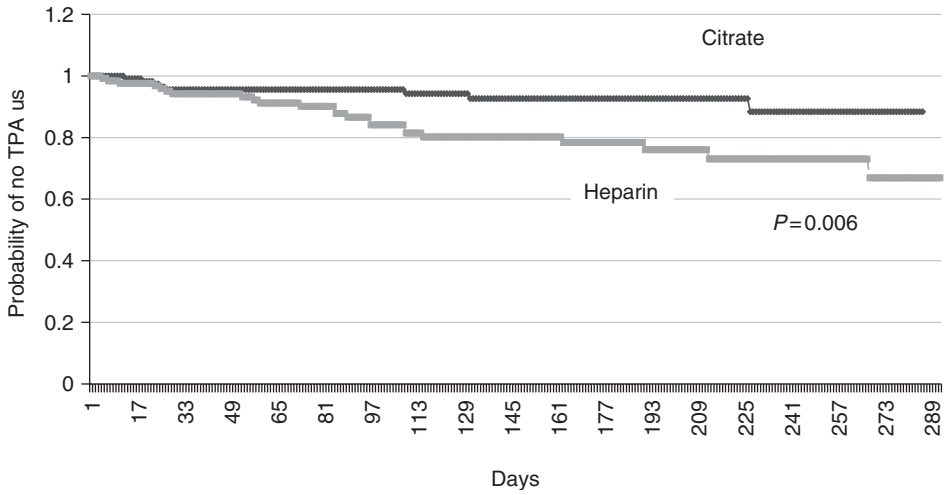

Fig. 2. Comparison of the time to TPA requirement in new catheters capped with heparin and citrate.

CVCs patency inserted in either the subclavian or internal jugular vein [23,24]. Hendrickx *et al*. [24] studied 10 patients who used citrate 5% lock while nine patients received heparin 5000 units/ml lock for 6 months. Based on a total of 1370 HD sessions, citrate 5% was comparable with heparin but the total number of clots (occlusive or non-occlusive) per dialysis session was significantly greater for the citrate (14.4%) *vs* the heparin (6.6%) lock group. Another study of citrate anticoagulation also noted clots in the dialyser (8.8%) but resulted in insignificant termination of dialysis (1.48%) [27]. Indeed, some nurses and patients in this study observed more obvious clotting, but this did not translate into functional abnormalities such as inadequate blood flow or greater need for thrombolytic therapy.

Buturovic *et al*. [23] evaluated 30 HD patients with temporary CVC who received locking with either citrate 4% (10 patients), heparin 5000 units/1 ml mixed with 2 ml normal saline (10 patients) or polygeline 3.5% (10 patients). There was no difference in the primary endpoints (volume of aspirated clot and removal of the catheter due to poor blood flow), but a low frequency of endpoint events (i.e. only one CVC per group removed due to clotting) was reported. Thus, a type II error (two groups considered equal but in fact are different) could not be excluded. Consistent with our findings, the citrate group also had a longer period of use (at least >20 days) compared with heparin or polygeline.

More recently, larger studies of citrate *vs* heparin locking have been performed in out-patient haemodialysis patients using tunnelled catheters. Plamondon *et al*. [25] performed a 4 week open label cross-over study of trisodium citrate 4% locking compared with heparin (5000 U/lumen) locking in 44 patients. Their primary endpoint was catheter thrombosis requiring intraluminal thrombolytic therapy. In contrast to our study (TPA use 3.3/1000 CVC days with citrate lock and 5.49/1000 with heparin lock), they found no difference using citrate (0.8%) or heparin (1.1%). This may be due to their shorter trial duration and fewer catheters such that the total catheter days were limited. Also, the cross-over design may have implications with regards to a lack of statistical and clinical independence of their data. Similarly, Weijmer *et al*. [7] did not find a difference in thrombolytic use between citrate 30% (4.11/1000 CVC days) and heparin (4.87/1000 CVC days) locks. However, the underlying finding of minimal outcome equivalency is consistent with our study.

Weijmer *et al*.'s [7] study was a randomized, multicentre trial of heparin (5000 U/ml) *vs* trisodium citrate 30% to determine whether there was a difference in catheter patency and catheter-related infections. The rate of CVC removal due to flow problems in the 30% citrate group was 3.2/1000 CVC days, compared with our rate of 1.65/1000 CVC days. Their higher removal rate may be due to broader criteria for premature catheter removal that included removal for infection, thrombosis, catheter breakdown or leakage, unintentional and accidental removals and the use of both temporary and permanent catheters. They found superior cumulative survival in catheters locked with citrate *vs* heparin with a median of ~180 and 85 days, respectively. By the end of our study, 25% of patients had their incident catheters removed/exchanged at a point estimate of 170 days (citrate lock) compared with 84 days (heparin lock) ($P = 0.042$).

Due to our low baseline infection rates, we were surprised to find a difference in catheter-related bacteraemias. However, previous studies of citrate +/− gentamicin locking have found a graded response with fewer infective episodes with increasing concentrations of citrate [28,29]. The difference in bacteraemia rate in this study should be interpreted with caution since a hospital policy instituting a nursing medical directive to apply a polyantibiotic ointment to the catheter exit site for catheter infection prophylaxis [30] was instituted during the study. Thus, the relative contributions of polyantibiotic ointment application and citrate 4% locking in reducing bacteraemia rates are unclear. A prospective study using citrate 4% capping with catheter-related infections as a primary outcome would clarify this issue.

In our institution, since the direct costs of citrate locking was less than heparin locking, and given the minimum equivalency of outcomes, the total cost benefit is likely greater if indirect costs were considered. The savings related to less thrombolytic use and fewer average hospital stays were not evaluated. Other studies, such as the one by Plamondon *et al*. [25] also found direct cost saving using citrate lock ($1.35 CAD) compared with heparin lock ($2.50 CAD). At the end of the study, our institution switched over to commercially available sterile, trisodium citrate 4% solution in 5 ml pre-loaded syringes (MEDXL Inc., Canada) that costs $1.05 per syringe. The main reason for the switch was convenience for the pharmacy. After trisodium citrate 4% is drawn up into 5 ml polyvinyl chloride syringes, it is chemically stable (up to 10% loss in the original concentration) for at least 28 days stored at room temperature (21°C) and protected from sunlight [31]. At our centre, the cost saving with citrate capping is ~0.63–0.96/lock, depending on whether it is commercially available or pharmacy prepared pre-filled syringes, respectively. In a programme that uses 100 catheters, this translates into cost savings of $10—15 000.00/year. This may not be applicable to other non-Canadian institutions as the availability and cost of citrate capping solutions may vary considerably.

This study has several clinical implications. Given the common problems with catheter malfunction, medical interventions for intra and inter-dialytic catheter anticoagulation are logical. Heparin is a standard choice for inter-dialytic catheter locking, but suboptimal doses are frequently used due to concerns of bleeding risks. Prior studies have noted greater haemorrhagic complications with low dose

heparin compared with even high concentrations of sodium citrate [19]. Even in critically ill patients with renal failure requiring continuous replacement therapy, the relative risk of haemorrhage has been reported to be less in patients receiving anticoagulation with citrate compared with heparin [32]. Increased bleeding risks were not found with citrate 4% use. The lower bleeding risk may be due to the shorter serum half-life compared with heparin. Overspill is known to occur when the volume of the catheter is 80% filled, with 15% spillage demonstrated with precise luminal volume instillation of an anticoagulant [33]. When heparin is used as the lock, ~2000 IU are injected into the patient when both sides of a two lumen catheter are filled with 5000 IU each [33]. While the amount of citrate leakage is unknown, when it enters into the systemic circulation, it is rapidly metabolized primarily by the liver to sodium bicarbonate [22,34]. In patients with normal liver function, the terminal serum elimination half-life is about 35 min, but is increased with liver disease [22,34]. Citrate clearance in HD patients is reported to be the same as non-dialysis patients [11]. Heparin has a longer serum elimination half-life of 60–90 min (but is unaltered by liver disease). Other safety concerns relate to citrate's ability to bind free ionized calcium, with the potential to cause hypocalcaemia and hypomagnesaemia, leading to cardiac dysrhythmias, seizures and bleeding [22,33]. High concentrations may also cause a 'metallic' taste in 10% of patients shortly after filling the catheter [35]. To date, our study inclusive, there have been no changes in serum calcium or magnesium or serious side effects with citrate 4% lock.

Our study had several limitations. It was not a prospective randomized blinded controlled trial. Sample size estimates for such a trial of adequate power to detect a difference in catheter patency would approximate 250–300 independent catheters per arm and was not feasible to perform in our institution. However, we determined a priori to prospectively compare predetermined outcomes and analysed independent groups of incident catheters that did not overlap study periods. We performed sensitivity analyses comparing only the first new catheter per patient per period and found similar results. These analyses were necessary from a quality assurance viewpoint; from daily clinical observations, the original perception of HD staff was that citrate was not different to heparin following conversion of locking solutions. Differences became apparent with analysis of incident catheters, highlighting the importance of objective appropriate analysis, and were necessary in order to implement change in inter-dialytic locking protocols. The economic evaluation was a basic one of direct costs only. A proper pharmacoeconomic evaluation was not performed. We estimate that the cost savings have been conservative and that the use of citrate would fall into the classic 'new treatment dominant' quadrant of standard incremental cost effectiveness ratio graphs [36].

Conclusions

Trisodium citrate 4% inter-dialytic locking has equivalent or better outcomes with regards to TPA use, need for catheter exchange, and access-related hospitalizations when compared with heparin locking. It is a safe and less expensive alternative to heparin locking of haemodialysis catheters. A large, randomized trial comparing heparin to trisodium citrate that includes a normal saline control group is needed to definitively resolve the issue of preferred locking solution for haemodialysis CVC.

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Conflicts of interest statement. None declared

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